July 1, 2019

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2018-D-4693: Postapproval Pregnancy Safety Studies

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments to the Draft Guidance on Postapproval Pregnancy Safety Studies.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO appreciates the FDA's efforts to develop the Draft Guidance on Post approval Pregnancy Safety Studies as it provides important information to both industry Sponsors and FDA reviewers regarding the FDA's views on safety monitoring after a product is approved. We support the objective of enhancing the medical community's knowledge of medicines' effects in these populations through the inclusion of safety information in product labelling.

BIO commends the FDA for welcoming the use of other types of post approval studies, beyond pregnancy registries for monitoring the safety of a product, especially those using electronic data sources. These newer sources of data can provide studies with greater power more quickly and may allow for several different comparator groups. However, as written, the majority of the Draft Guidance is focused on pregnancy registries, implying that registries are the default mechanism for conducting pregnancy surveillance in the post-marketing setting. For example, the Draft Guidance refers to other types of pregnancy surveillance studies as "complementary" and discusses the strengths and limitations for pregnancy registries (Section IV); however, there is no discussion of strengths and limitations for electronic data sources, population-based surveillance, or population-based case control studies. Additionally, the Draft Guidance recommends that protocols should include a statistical analysis plan and a description of target sample size based on power calculation only for pregnancy registries; however, this recommendation should apply to other type of studies (e.g., insurance claims data) as well.

As the FDA is aware, pregnancy registries often take 10 years or more to conduct, significantly limiting their utility in informing the risks of exposure during pregnancy. Furthermore, they often encounter difficulty when recruiting and enrolling an adequate number of patients. With these limitations in mind, the FDA may consider amending this guidance and balancing discussion of all possible methods of pregnancy surveillance,

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including the use of retrospective studies using electronic data sources and real-world evidence, the strengths and weaknesses of each approach, statistical considerations, and the circumstances under which it is appropriate to utilize each approach.

BIO also requests that the FDA consider referencing the need to making better scientific use of existing systems to collect and evaluate pregnancy information, such as enhanced pharmacovigilance studies. Such studies can capture information on all pregnancies exposed to a drug focusing on collecting data prospectively (e.g., when the pregnancy is reported either before the end of pregnancy or before the detection of a congenital malformation), in a way that resembles a registry. The aim would be to provide a denominator and full and consistent data through a clear follow-up schedule with repeated attempts to obtain and correct data. In order to support increased consistency among studies, and therefore be able to use data from several registries to contextualize the findings from registries studies, there is a need to standardize definitions and to align among public partners, service providers and regulatory authorities.

BIO appreciates this opportunity to submit comments on the Draft Guidance on Postapproval Pregnancy Safety Studies. We provide additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Danielle Friend, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

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I. INTRODUCTION		
Lines 26-39	Drug utilization and mechanism of action studies can help in the planning of pregnancy studies to obtain safety information. Mechanism of action studies can guide us on choosing which maternal and infant outcomes should be evaluated and drug utilization studies can help determine if pregnant women are taking the drug, if there will be power to conduct studies, and what the best comparator(s) will be.	BIO requests that the FDA reference drug utilization and mechanisms of action studies in the introduction of the Draft Guidance.
II. BACKGROUND		
Lines 79-81	This section indicates that "based on FDA reviews and the 2014 public meeting, FDA understands that pregnancy registry data have contributed to labeling changes and clinical guidelines, but their potential has not been fully realized, often because of feasibility issues," however, registries lack ability for a number of reasons and will never be "fully realized".	BIO requests the following edit: "Based on FDA reviews and the 2014 public meeting, FDA understands that pregnancy registry data have contributed to labeling changes and clinical guidelines, but their potential **is limited, one challenge being** ~~**has not been fully realized, often because of**~~ feasibility issues."
Lines 94-106	In this section the FDA references several types of postmarket studies and indicates that the listed approaches are not intended to indicate a hierarchy of evidence; however, by calling other types of studies "complementary" it appears to the reader that registries are first in the hierarchy. To our understanding from the following sentence, this is not intended: "These approaches are not intended to	BIO requests that the FDA divide the approaches by primary source of data collection and secondary source of data collection and use different wording other than "complementary."

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	imply a hierarchy of evidence from the different study methods." Instead of dividing the guide into registries and complementary, we suggest dividing the approaches by primary source of data collection and secondary source of data collection.	
III. PHARMACOVIGILANCE — CASE REPORTS AND CASE SERIES		
Entire section	It might be beneficial to break this section into traditional pharmacovigilance and enhanced pharmacovigilance scenarios, where all prospective cases are included in a way that resembles a registry. For each approach it would also be helpful to include the strengths and weaknesses.	BIO requests that the FDA divide this section into traditional pharmacovigilance and enhanced pharmacovigilance scenarios and provide strengths and weaknesses for each approach.
Lines 131, 140	This section lists critical factors in evaluating the effects of product exposure in human pregnancies.	BIO requests that the FDA also reference medication/medical/environmental exposures/genetics related to paternal as information that might also be helpful to collect.
Line 149-151	In this section, the FDA indicates that "case reports have been most useful and influential in situations where the adverse pregnancy outcome rarely occurs as a background event, and the adverse outcome is well-documented." This section would be strengthened by the addition of examples.	BIO requests that the FDA provide examples or add footers with reference to examples of rare pregnancy outcomes that have been identified via case reports alone.
Lines 158-160	Routine pharmacovigilance (i.e., ADR reporting, individual case review, signal detection activities) can evidence a reasonable possibility of a causal relationship between product exposure and an event.	BIO requests the follow edit: "Thus, because of the limitations of post-marketing data, routine pharmacovigilance usually will be insufficient for a

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	In general, routine pharmacovigilance is insufficient to quantify risk.	conclusive assessment regarding the potential risk of an exposure during pregnancy because of the inability to ~~**quantify risk**~~ **establish a causal association.**."
Line 167	Pregnant women should be able to decline participation or additional follow up at any time at their description.	BIO requests that the FDA clarify whether FDA is proposing a "pregnancy surveillance program" for post-marketing pregnancy cases (maternal and paternal exposures) where both men and women need to consent to participation.
IV. PREGNANCY REGISTRIES		
A. Overview		
Lines 185-188, 328-329	Worldwide pregnancy surveillance data may not be captured systematically or comprehensively, thus limiting the ability of the sponsor to provide this data. Additionally, it is not clear what the FDA considers "worldwide safety data collection."	BIO requests the following edits: "When submitting interim and final pregnancy registry study reports, sponsors **may** ~~**should**~~ include cumulative analyses of worldwide pregnancy surveillance data**, when available,** to provide perspective on registry feasibility and updates on available safety data in pregnant women that may not be included in the registry." BIO also requests that that FDA clarity was is meant by world-wide safety data collection
Line 174	In this section the FDA refers to prospective and retrospective studies, but definitions for each have not been included.	BIO requests that the FDA include definitions for prospective and retrospective in the context of pregnancy registries.
Lines 193	This section indicates that "By enrolling women exposed to the product of interest, pregnancy registries can be an efficient way to collect data on the effects of rare exposures during pregnancy."	BIO requests that the FDA eliminate this bullet.

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	However, the conduct of pregnancy registries often indicates that rare exposures are the reason for most pregnancy registries failing.	
Lines 195-197	This section indicates that "A pregnancy registry can be initiated and start to accrue real-time data as soon as a product becomes commercially available, in contrast to the use of claims data and electronic health records where there will be a lag time in data availability." However, the issue is not when real-time data starts to accrue after product launch, but when the data are sufficient to test hypotheses. For example, collecting 20-30 cases per year in a pregnancy registry does not show any advantage in generating faster results, versus efficiently leveraging resources and conducting a safety study when there's sufficient power for hypothesis testing. Given this, BIO does not believe that this bullet should be considered a strength of a pregnancy registry.	BIO requests that the follow edit: "~~**A pregnancy registry can be initiated and start to accrue real-time data as soon as a product becomes commercially available, in contrast to the use of claims data and electronic health records where there will be a lag time in data availability.**~~"
Lines 199-205	There are two strengths of pregnancy registries outlined in lines 199-205; however, they are redundant.	BIO suggests collapsing the bullets into one bullet that states: "**Prospective enrollment facilitates ascertainment of accurate information about whether exposure occurred and the timing of the exposure in relation** …."
Line 207	This "strength" (collecting data on variety of pregnancy and infant outcomes) is not unique to pregnancy registries. Additionally, the second listed limitation minimizes this supposed strength by	BIO requests that the FDA add examples to the variety of pregnancy and infant outcomes that FDA believes are strengthened by studying through a pregnancy registry.

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	indicating that "effects on less common, specific major congenital malformations (MCMs) may be missed". Many MCMs are considered rare events, which may limit the primary data collection approach (e.g., used in pregnancy registries) as the optimal and most efficient study design.	
Lines 207-208	This section indicates that "A pregnancy registry can potentially collect data on a variety of pregnancy and infant outcomes, including postnatal outcomes," but does not provide information on the definitions or inclusion criteria of a pregnancy versus a pediatric registry.	BIO requests that the FDA provide definitions in the Draft Guidance for pregnancy versus pediatric registries as well information regarding possible inclusion criteria for each.
Line 215	This section of the Draft Guidance lists limitations to pregnancy registries, however there are several additional limitations that should be added.	BIO requests that the FDA include the following limitations in the finalized guidance: • Availability of pregnancy registry data is dependent upon the uptake of the product • Registries are subject to selection bias, women who enroll are often different than those who do not with regard to education, economic status, etc. • Pregnancy registries rely on self-reported data, there is a need to validate this via medical record and some registries do not have the capability to do this. • Pregnancy registries may take a long time to meet sample sizes that provide meaningful information to prescribers and patients. • Interpretation of insufficient sample sizes is challenging

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Lines 220-222	This section indicates that "Most pregnancy registries are designed primarily to collect data used to assess the overall risk of MCMs. Effects on less common, specific MCMs may be missed for all but the most potent teratogens," however, another reason is due to small sample size, less common malformation will not have sufficient power.	BIO requests the follow edit: "Most pregnancy registries are designed primarily to collect data used to assess the overall risk of MCMs. Effects on less common, specific MCMs may be missed because of **small sample sizes,** for all but the most potent teratogens."
B. Registry Design Considerations		
Lines 248-252	This section indicates that pregnancy registries can be used as signal detection studies and generate hypothesis; however, a pregnancy registry is not an efficient approach for signal detection. There are other approaches to consider for signal detection, including the enhanced pharmacovigilance or proactive safety monitoring. Additional clarity and comments are needed for when and under what criteria a pregnancy registry would be used for signal detection.	BIO requests that the FDA provide examples of the circumstances in which a pregnancy registry would be considered signal detection.
Lines 268-269	It is very difficult, if not impossible, to evaluate the presence or absence of MCM in all non-live births, particularly miscarriages or elective terminations, as these assessments are not part of routine clinical practice.	BIO requests the follow edit: "~~**Within each of these categories**~~ **In some cases** the fetus or infant can be evaluated for the presence or absence of the primary outcome."

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Lines 267-268	In this section the FDA indicates that the type of pregnancy outcomes.	For clarity, BIO requests that the FDA separate live births into term and pre-term. Additionally, if a miscarriage is defined as loss before 20 weeks, fetal death/stillbirth after 20 weeks, BIO requests that the FDA indicate that if the loss is at 20 weeks it should be included in fetal death/stillbirth.
Lines 271-272, 278	In this section the FDA includes criteria for defining birth defects; however, abnormalities and malformations definitions have the potential to be interpreted differently across studies and can make it difficult to compare and interpret studies.	For clarity and consistency, BIO requests that the FDA reference the EUROCAT classifications as categories for abnormalities and malformations.
Lines 285	This section states that "Measures of fetal growth deficiency (small for gestational age)," however, other parameters such as length and head circumference are also measured in newborns.	BIO requests the following edits: "Measures of fetal growth deficiency (**e.g.,** small for gestational age)."
Line 286	This section outlines examples of other outcomes that may be primary or secondary on a case-by-case basis but does not include gestational age at birth as an outcome.	BIO requests that gestational age be added to the list of primary outcomes.
Line 290	For ease of estimating a sample size, there could be a consensus on which rates to use from the general population for major malformation, miscarriages, etc. It would be useful to have single standard from FDA to complete this activity.	BIO requests that the FDA define a common standard for adverse pregnancy outcome rates.
Lines 319-330	In Section 5. Safety Evaluation When a Pregnancy Registry is not Feasible, the Draft Guidance states "In	BIO requests that the FDA indicate that as many products are rarely used during pregnancy, consideration should be given during discussions with the sponsor whether a

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	some situations, a pregnancy registry may never have the power to allow statistical inference…..”	pregnancy registry is not feasible (apriori) or systematically monitoring the product use among pregnant women and conduct a pregnancy study once a threshold of product use has been achieved.
Line 320-325	This section indicates that “Achievement of an adequate sample size may not occur when the likelihood of exposure in pregnancy is low or use of a product is not recommended during pregnancy,” but lacks detailed on what is considered “low”. The FDA indicates that “For products that are anticipated to be used rarely during pregnancy (e.g., treatment of advanced cancer), sponsors can consider a pregnancy surveillance program (a structured approach for data collection with targeted questionnaires to obtain follow-up information on all exposed pregnancies of which sponsors become aware),” however, the FDA does not provide any additional detail regarding such pregnancy surveillance programs. One difficulty with registries is that sample size cannot always be anticipated when the protocol is being developed as it largely depends on how the product is used.	BIO requests that the FDA expand upon this section to include the concept of a pregnancy surveillance program, when such programs would be appropriate, including guidance on building an acceptable justification for not pursuing a pregnancy registry, and how it would differ from routine surveillance as mentioned in the Guidance. BIO also requests that the FDA make clear when an exemption from associated postmarketing registry studies would be acceptable. BIO requests that the FDA provide additional detail regarding what is considered “low” in terms of the number of women exposed. BIO requests that the FDA indicate in the Draft Guidance, their willingness to consider feasibility before initiating a pregnancy registry especially in circumstances where the registry will likely not achieve adequate sample size.
Lines 513	In this section the FDA indicates that “Patient-initiated recruitment efforts rely on patients to contact the registry study staff and self-enroll. Because pregnancy is often recognized by the patient first, registries that enroll patients directly can allow for recruitment of patients earlier in pregnancy.”	BIO requests the following edit: “Patient-initiated recruitment efforts, **when allowed and appropriate,** rely on patients to contact the registry study staff and self-enroll. Because pregnancy is often recognized by the patient first, registries that enroll

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	However, while self-enrollment or pre-registration is indeed an option in the U.S. it is not one for a global registry, particularly in Europe where it may be legally precluded by privacy laws and other regulations.	patients directly can allow for recruitment of patients earlier in pregnancy."
Line 550	This section indicates that "interim data reports to participating health care providers may bolster retention," but the FDA provide no guidance regarding how these interim data reports may be made available.	BIO requests that the FDA provide details regarding how sponsors should provide interim data reports to the public. For example, where is it appropriate to publish these interim data reports (i.e., abstract) or publicly display (i.e., clintrials.gov, ENCEPP, sponsor registry website)?
Lines 565-575	In this section, the FDA indicates that "FDA encourage sponsors to work together directly or through consortiums to develop or support multiproduct registries."	In order to encourage such an approach, BIO requests that FDA provide guidance on enrolling women into multiproduct pregnancy registries, as enrollment of patients will likely mimic the product market share and will be a challenge for newer products with less market share. The study will likely not be powered sufficiently to draw any meaningful conclusions for the newer products.
Lines 588-597	The choice of source data to use can be driven by the outcome to be characterized and the expected effect size. - If a small sample size can efficiently categorize a critical risk, then a pregnancy registry should be considered. - If a large sample size is required but the uptake of the drug under investigation is expected to involve a very limited number of patients (e.g., rare disease or a biomarkers-driven sub-population), then a pregnancy	We request that FDA add the adjacent bullets to the guidance.

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	registry might have to be embedded within a disease registry to have a chance of identifying patients - If the outcome to be identified is rare then a bigger sample size might be needed, and secondary source of data might be more adequate to evaluate the safety of the drug.	
Line 591-592	This section indicates that "...on the safety of drugs and biological products during breast feeding." This statement is not an inclusive/accurate way of acknowledging varied feeding options (i.e., women may exclusively pump breast milk, rather than bottle feed).	BIO requests the following edits: "... safety of drugs and biological products ~~during breast-feeding~~ to infants fed breastmilk"
Line 593	This section indicates that "... recruit and enroll breast-feeding women..." This inclusion criteria needs to be broadened. For example, women need not be breastfeeding to enroll, they only need to be lactating.	BIO requests the following edit: "...recruit and enroll ~~breastfeeding~~ **lactating** women…"
V. COMPLEMENTARY STUDIES		
Lines 605-609	States: "Thus, additional studies that complement data obtained from pregnancy registries and other sources, referred to as complementary studies in this guidance, can be implemented as the need arises to better understand the specific effects of using a drug or biological product during pregnancy, and to more precisely quantify the magnitude of an association	BIO request that the FDA provide additional guidance and comments on the criteria that should be used when choosing a fit for purpose pregnancy safety study.

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	between a pregnancy exposure and a specific outcome". It is unclear from the guidance when and how sponsor can discontinue registry study. A fit for purpose approach should be considered in determining the most optimal study design to evaluate the objectives of a pregnancy safety study. A pregnancy registry is a study design option to consider, however it may not be the most feasible study design, especially with the significant challenges in patient's enrollment and other operational/clinical challenges.	
Lines 611-612	This section indicates that "Complementary studies can be retrospective in design, using secondary data…," however, this is not always the case. A cohort study may be equivalent to a prospective study, but case control studies are generally conducted in a retrospective nature. However, a case control study can be designed to be prospective in nature.	BIO requests that the FDA clarify this point.
Line 620	This section indicates that "These data sources and designs are discussed in the following subsection," however, it fails to mention other data sources that may contribute.	BIO requests that the FDA reference the Sentinel data network, MyStudies app, and social media in contributing to the collective body evidence to evaluate pregnancy and congenital outcomes, beyond supporting recruitment efforts. This is critical as FDA further defines and issues guidance on the use of RWD/RWE and digital innovation, including artificial intelligence.

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A. Electronic Data Sources		
Lines 629, 633	The date of last menstrual period would be more useful than the estimate of conception.	We propose adding this parameter to the guidance.
Lines 657-659	While the challenges of estimating non-live births and associated gestational age in database studies is an important point, the ability to identify non-live births also represents a potential advantage of database studies over traditional pregnancy registries. In pregnancy registries, early non-live births are often missed due to enrollment occurring later in the pregnancy. In fact, there is evidence that claims databases may have more complete capture of non-live births than registries (Yusuf et al 2018)[1].	This point could be addressed as a potential strength of alternative (i.e., other than registries) study designs. Alternatively, the paragraph on line 657 could begin with, "**EHD may provide more complete capture of non-live births than pregnancy registries (Yusuf et al). However,** use of EHD to identify..."
Lines 674	Dates from pregnancies utilizing assisted reproductive technology, e.g. *in vitro* fertilization, would be another useful method for identifying gestational age.	BIO requests the following edit: After line 674 insert: "**Timings when reproductive technology is utilized (e.g. *in vitro* fertilization).**"
Lines 715-723	It is important to recognize that validation does not need to occur in the same database or in the same population.	Recommended change: Add the text in red to Lines 715 and 723 "…in the specific **(or similar)** database…"

[1] Yusuf, A., Chia, V., Xue, F., Mikol, D. D., Bollinger, L., & Cangialose, C. (2018). Use of existing electronic health care databases to evaluate medication safety in pregnancy: Triptan exposure in pregnancy as a case study. *Pharmacoepidemiology and drug safety*, *27*(12), 1309-1315.

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B. Population-Based Surveillance and National Registries or Registers		
Lines 745	A significant challenge of registries monitoring for rare and infrequent events if the sample size of the population being monitored.	BIO requests that the FDA indicate in this section that pregnancy studies which are linked globally rather than nationally or regionally can offer increased power.
Line 752	Vaccine and Medications in Pregnancy Surveillance Systems (VAMPSS) (United States)	BIO suggests that the FDA reference that VAMPSS is conducted as a single study arm for population surveillance. The second arm of VAMPSS uses a pregnancy registry approach.
C. Population-Based Case Control Studies		
REFERENCES		
APPENDIX A: LIST OF DATA COLLECTION ELEMENTS		